REMARKS

Applicants have amended claim 23 to better capture the envisioned commercial embodiments. The specification supports the claim amendment, thus the claim amendments do not introduce new matter to the application.

The Cited Art Does not Render the Claimed Invention Obvious

The Office Action of 14 November 2008 rejected claims 23 and 27-48 under 35 U.S.C. §103 as allegedly being unpatentable over Marler, in view of Bent, Agerup, Vanderhoff, The Merck Index and Hawley's Chemical Dictionary. Applicants respectfully disagree with the Office Action and assert that the claims are not obvious in view of the cited art. Applicants respectfully disagree and request that the Examiner reconsider and withdraw the obviousness rejection in view of the comments below. Applicants reiterate and incorporate by reference the arguments presented in the previous response to office action, filed 13 August 2008.

Applicants remind the Office that the currently claimed methods are directed towards the use of microparticles of cross-linked alginate, wherein the microparticles of alginate are crosslinked with a divalent or polyvalent cation, and wherein the alginate has a molecular weight of between about 100kDa and about 1200kDa.

It should be noted that none of the cited references teach or suggest the use of alginate with the specified molecular weight, and it is axiomatic that the cited references must teach each and every element of the claimed invention to establish a case of *prima facie* obviousness. Therefore, the cited references can not, by law, render the claimed invention obvious. To account for this lack of disclosure amongst the cited references, the Examiner states that "[e]ven though the prior art of record does not suggest a molecular weight range for the alginate one of skill in the art would optimize the molecular weigh of the alginate in order to obtain maximum beneficial effects. Such optimization is routine in the art." Thus, the Examiner is filling in the missing elements by asserting that routine optimization is all that is required to render the invention obvious in view of the cited art.

Again, Applicants disagree. To establish a *prima facie* case of obviousness by asserting that routine optimization of a variable is all that is required, the prior art must recognize the variable as a result-effective variable. Moreover, Applicants assert that more is required from the Office to establish obviousness than just a mere assertion that something is "routine optimization." Indeed, the MPEP states that "[a] particular parameter must first be recognized as a result-effective variable, *i.e.*, a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation." MPEP §2144.05 (emphasis added) (citing *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977)). Applicants assert that the Examiner has not established that the molecular weight of the alginate used in the cited art methods is recognized as a result-effective variable.

The alginate used in the methods of the claimed invention should possess long-term stability and be injectable for increasing tissue volume. The methods require injection of the material. Given that the material is being injected, it is ideal that the material be stable over a period of time in order to ensure that long-term aesthetic effects are achieved. Again, because the alginate is being injected, the material should be highly pure and possess low level toxicity. None of the references teach that increasing the molecular weight of alginate would be effective to increase its stability and/or decrease its toxicity. Marler, Bent and Vanderhoff only disclose commonly used, low molecular weight alginate, and none of the references teach or suggest augmenting the molecular weight of the alginate because the molecular weight of the alginate is a result-dependent variable.

It should be noted that the purified inventive material with the given molecular weight exhibits significantly improved properties (in particular long term stability) as compared to the alginate material used in the methods disclosed in the cited art. Interestingly, it is the present Applicants that, for the first time, identified the molecular weight of alginate as a relevant parameter for increasing long term stability.

Comparative experiments substantiate this finding that increasing the molecular weight of alginate aides in increasing the stability. Marler reports that, 8 weeks after injection, approximately 30% of the implant volume is maintained. Moreover, additional publications in the field obtain comparable values as those reported in Marler, and also report that the implanted alginate material is completely degraded in about 12 to 14 weeks after injection. Indeed, Bent *et al,* which the Office cites in the present office action, at page 158, states that "[t]he gel serves as a substrate for injectable delivery, and then degrades."

In addition, the cited prior art methods that try to provide highly purified alginate never provide an alginate with a molecular weight of more than 100kDa. Instead the cited references only provide for a much lower molecular weight alginate. Moreover, the state of the art at the time of filing actually refers to the mannuron/guluron acid ratio of alginate material as the determining parameter for its *in vivo* stability thereby ignoring the molecular weight of the alginate. For example, Mancini *et al,* which is appended to this response, explored *in vivo* characteristics, including stability, and focused primarily on the mannuron/guluron ratio and completely ignores the relevance of the molecular weight of the alginate. Thus, the only thing that the cited art could possibly motivate one to optimize would be the mannuron/guluron acid ratio of the alginate material in an attempt to increase the long-term stability of the implant. Nothing in the cited art suggests that the molecular weight of the alginate would be crucial for increasing the stability.

In contrast, the claimed methods are directed towards the use of microparticles of cross-linked alginate, wherein the alginate has a molecular weight of between about 100kDa and about 1200kDa. Applicants have implanted the claimed material, which maintains its volume of up to 90% even after 6 months of implantation. Indeed, all implanted beads (100%) were identified after 6 months, with their total weight corresponding to about 85 to 90% of the initial weight, and with the bead diameters corresponding to more than 95% of the initial values. The art does not teach or suggest the claimed molecular weight parameter and the art does not recognize that one would be able to optimize stability based on the molecular weight of the alginate.

With regards to the purity of the alginate, the purification methods in the cited art will necessarily result in at least a partial degradation of the alginate glycoside chains, thereby dramatically reducing the molecular weight to values even further below 100 kDa. Indeed, the products disclosed in Marler, as well as products like Pronova Biopolymers (Oslo, Norway) consist of alginate material with a molecular weight of less than 100kDa.

In short, the Examiner has not established that the claimed invention is obvious because the cited references do not teach all the limitations of the claimed invention and the cited art does not recognize the molecular weight of alginate as a result dependent variable. Applicants' position is fortified by *Ex parte Whalen*, 89 USPQ2d 1078 (Bd. Pat. App. & Int. 2008), a recent precedential decision of the Board of Patent Appeals and Interferences (BPAI), a copy of which is appended hereto. The facts in *Whalen* are remarkably similar to those of the present application, and the Board agreed with applicants that the examiner had not established a case of *prima facie* obviousness.

In *Whalen*, the examiner rejected claims for embolizing an aneurysm at a vascular site comprising the use of a biocompatible polymer, where the biocompatible polymer had a "molecular weight sufficient to impart ... a viscosity of at least about 150 cSt ... ." *Ex parte Whalen,* 89 USPQ2d at 1079. The examiner in *Whalen* cited three prior art documents (Evans, Greff '767 and Taki), but none of the references recited a viscosity limitation of the polymer. To fill in this missing requirement, the examiner asserted that "a person of ordinary skill in the art 'would have been motivated to optimize the viscosity of the Evans' ... final formulations, because he would have had a reasonable expectation of success in achieving the safest clinical outcome ... ." *Ex parte Whalen,* 89 USPQ2d at 1083.

In addressing this obviousness rejection, the Board stated that

> [t]he Examiner has not made out a prima facie case that the claimed compositions would have been obvious based on the teachings of Evans, Greff '767, or Taki. While 'the discovery of an optimum value of a variable in a known process is normally obvious,' *In re Antonie,* 559 F.2d 618, 620 [195 USPQ 6] (CCPA

> 1977), this is not always the case. One exception to the rule is where the parameter optimized was not recognized in the prior art as one that would affect the results. *Id.*
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> Here, the Examiner has not pointed to any teaching in the cited references, or provided any explanation based on scientific reasoning, that would support the conclusion that those skilled in the art would have considered it obvious to 'optimize' the prior art compositions by increasing their viscosity to the level recited in the claims. No reason to have done so is apparent to us based on the record. On the contrary, the references all suggest that low viscosity was a desired property in embolic compositions. ...
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> ...
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> Thus, the references teach that low viscosity is a desirable characteristic for embolic compositions. In our view, none of the cited references would have led a person of ordinary skill in the art to modify the known embolic compositions by increasing their viscosity to at least 150 cSt at 40°C. The Examiner has not adequately explained why such a modification would have been obvious.

Ex parte Whalen, 89 USPQ2d at 1083-1084 (emphasis added). It is noteworthy that the Board actually *reversed* the examiner to reach a conclusion of non-obviousness, based on the facts before it.

Turning to the issue of covalent crosslinking versus ionic crosslinking, Vanderhoff explicitly emphasizes that covalent cross-linking is strongly preferred and, in fact, discourages the reader from using ionic crosslinking. Indeed, Vanderhoff discusses using calcium ions to cross-link the alginate, but that "ionic bonds may be broken down by a change in external conditions, *e.g.*, by chelating agents. On the other hand, covalent bonds are stable in the presence of chelating agents. Thus, the most preferred cross linking agent for use in the practice of the invention is one that forms covalent bonds ... rather than ionic bonds." Vanderhoff, page 9, lines 30 – page 10, line 4. Thus, the Examiner's own reference teaches away from the ionic bonds used in the claimed methods. The Board's analysis in *Whalen* in view of the Supreme Court's *KSR* decision is also instructive in the current situation.

> ... when the prior art teaches away from the claimed solution as presented here ..., obviousness cannot be proven merely by showing that a known composition could have been modified by routine experimentation or solely on the expectation of success; it must be shown that those of ordinary skill in the art would have had some apparent reason to modify the known composition in a way that would result in the claimed composition.

Ex parte Whalen, 89 USPQ2d at 1084.

Even disregarding the explicit teaching away in Vanderhoff, the present invention is further distinguished from Vanderhoff by at least two additional ways. First, Vanderhoff cannot possibly be using ionic linkers, since the molecular weight of the alginate material is much lower than the alginate material presently claimed. Thus, even though Vanderhoff mentions ionic bonding, albeit in a negative light, it is clear to one of skill in the art that Vanderhoff would not be applicable for ionic crosslinking of higher molecular weight alginate. In addition, Vanderhoff must use additional covalent crosslinking procedures for his low or medium molecular alginate (of considerably less weight than 100kDa) to confer at least a minimum stability to his alginate material. In other words, Vanderhoff's covalent methods are more complicated that the present ionic methods.

Moreover, covalent crosslinking has at least two major disadvantages. First, the cross-linkers disclosed in Vanderhoff, page 9, line 25 are toxic and mutagenic, making it almost impossible to use covalently crosslinked material for *in vivo* products. Second, if used at all, the process of covalently crosslinking the alginate must be carried out *in vitro* which does not allow for any (therapeutically desired) *in situ* crosslinking. In particular, the covalent crosslinkers in Vanderhoff usually retain their chemical reactivity *in vivo* and thus can be mutagenic. Thus, one of skill in the art would not look to Vanderhoff to prepare compositions to be injected into living subjects. In addition, Vanderhoff also requires a complicated emulsion-based production process for allowing the kinetically slow covalent crosslinking to occur, whereas a totally different process provides the microbeads of the present invention. The differences in the production process in Vanderhoff and for the compositions used in the claimed methods are not trivial, since

the production process in Vanderhoff leads to further issues, such as impurities (remainder of the emulsifier) and toxicity. Thus, the present invention dramatically simplifies the crosslinking methods in Vanderhoff. As an added byproduct, the present methods beneficially result in a less toxic product that can actually be crosslinked *in situ*, after injection, which further simplifies any injection methods previously known in the art. Finally, it should be noted that covalently crosslinked polysaccharides are degraded *in vivo*, which leads to smaller crosslinked fragments, which, in turn, usually evokes undesired side effects.

These problems plaguing the art, particularly with respect to impurities, were discussed in the previous response. In reply, however, the Examiner dismissively states that "[i]mpurities can be removed by purification." *Office Action*, page 8. But the Examiner provides no reasoning or basis as to how one would go about removing the impurities in the prior art compositions. Examination requires more than simply dismissing Applicants' arguments without reason. In fact, there is no teaching in the cited art as to how the alginate material would have to be purified and what kind of characteristics would be required for stable implantation. Applicants invite the Examiner to explain how one of skill would perform the methods of the prior art and then purify the final product to decrease the toxicity associated with the Vanderhoff methods.

All these problems with the prior art alginates (of a lower molecular weight and covalently crosslinked) are overcome with the present invention. Indeed the cited art[1] does not even hint, let alone suggest or teach, the use of the inventive alginate material with a molecular weight of at least 100kDa that is ionically crosslinked. Applicants have therefore invented a more stable alginate composition that is also safer *in vivo*. The present invention also allows for ionic crosslinking of the injected liquid alginate material *in situ*, which is much more therapeutically beneficial.

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[1] Agerup, which is also cited against the present claims, also fails to cure the deficiencies of the cited art of record. Agerup is completely different from the subject matter currently claimed, since Agerup uses dextranomeric microbeads for tissue augmentation, as the Office Action establishes. Furthermore, Agerup fails to teach the use of high molecular weight alginate, even as a carrier for the dextranomer.

Accordingly, Applicants assert that the references, alone or in combination, do not teach injection of cationic cross-linked alginate to increase tissue volume. In fact, based on the collection of art that the Examiner has cited, the best that one would hope to achieve would be a low molecular weight alginate that is covalently crosslinked and possess a myriad of stability and toxicity issues. Nothing in the art would direct, guide or motivate one of skill in the art to (a) increase the molecular weight of the alginate and (b) use ionic crosslinking procedures to arrive at the claimed invention. Moreover, based on Vanderhoff's disclosure alone, one of skill would not have an a priori reasonable expectation of success in using ionically crosslinked alginate. Thus, the references can not be combined to render obvious the presently claimed invention. Moreover, there is no reason of record as to why one of skill in the art would "optimize" the molecular weight parameter or choose ionic binding over covalent bonding, in light of Vanderhoff teaching away from using ionic methods. Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, he or she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Date 13 February 2009 By _____

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